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(54) HEMOLYSIS DETECTION DEVICE, SYSTEM AND METHOD

HÄMOLYSEERKENNUNGSVORRICHTUNG, -SYSTEM UND -VERFAHREN

DISPOSITIF, SYSTÈME ET PROCÉDÉ DE DÉTECTION D'HÉMOLYSE

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(56) References cited:
WO-A1-95/10044
WO-A1-2011/040874
WO-A1-2012/036622
WO-A1-2013/085462
DE-T2- 69 432 122
US-A- 5 593 638
US-A1- 2012 275 955
US-A1- 2012 277 697

- **'Vivid Plasma Separation Membrane' PALL LIFE SCIENCES 2009, pages 1 - 6, XP055371628 Retrieved from the Internet: <URL:https://www.pall.com/pdfs/OEM-Materials-and-Devices/09.2730_VividP)asma_DS_6pg.pdf > [retrieved on 2015-11-22]**
- **SARAH WEBB: 'Low-Cost Device Quickly Isolates Blood Plasma' C&EN 15 October 2013, XP055371633 Retrieved from the Internet: <URL:http://cen.acs.org/articles/91/web/2013/10/Low-Cost-Device-Quickly-isolates.html> [retrieved on 2015-11-22]**

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to diagnostic testing, and more particularly to devices, methods, and systems for rapidly scanning samples for hemolysis prior to subjecting the same samples to one or more analytical tests.

BACKGROUND OF THE INVENTION

[0002] Point-of-care testing refers generally to medical testing at or near the site of patient care, such as in an emergency room. A desired outcome of such tests is often to obtain rapid and accurate lab results to determine a next course of action in patient care. A number of such point of care tests involve taking or otherwise using a blood sample from a patient. The ideal blood sample is pure plasma separated from the source whole blood sample. Hemolysis (haemolysis), however, is a common problem which may introduce undesirable components into the plasma fraction.

[0003] In particular, hemolysis refers to the rupturing of erythrocytes (red blood cells) and the release of their contents, including hemoglobin and potassium, into surrounding fluid (e.g., blood plasma). Hemolysis may occur in vivo or in vitro (inside or outside the body). During any of the collection, transportation, and handling of patient whole blood samples, there is the possibility of hemolysis. If hemolysis occurs, the resulting components in the sample may cause interference in a number of tests, thereby leading to a signal reduction, reduced measurement accuracy and precision, or to false positive results at the other end of the spectrum. Further, if hemolysis occurs, it has been found that the potassium concentration in a corresponding sample may increase significantly and cause a high risk of misdiagnosis in a diagnostic test for potassium levels. See Clinical Chemistry, December 2003, vol. 49, no. 12, 2105-2106. Current methods do not adequately and quickly determine whether an unacceptable level of hemolysis has occurred in a blood sample. For example, WO 95/10044 is directed to a method of detecting hemolysis in a whole blood sample. A visual detection of hemolysis by means of detection compartments is further provided in WO 2013/085462 A1 and WO 2011/0408074 A1.

[0004] From WO 2012/036622 A1 a testing system is known for analyzing a risk of developing organ failure. Systems and methods for delivering to and/or receiving fluids or other materials from subjects, in particular from the skin of a subject, are disclosed in US 2012/0277697 A1.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] The invention is explained in the following description in view of the drawings that show:

FIG. 1 illustrates a device for hemolysis detection in a sample in accordance with an aspect of the present invention.

FIG. 2 illustrates a system for hemolysis detection in a sample in accordance with an aspect of the present invention.

FIG. 3 is a graph showing a decrease in detector output signal as a function of increasing hemolyiss.

DETAILED DESCRIPTION OF THE INVENTION

[0006] Aspects of the present invention are directed to devices, systems and methods that enable the quick and reliable detection of hemolysis in a sample such that a sample which exhibits an unacceptable level of hemolysis can be immediately flagged or disregarded in an associated diagnostic test. In this way, via the devices, systems, and methods described herein, a sample may be rapidly tested to determine whether hemolysis has occurred and a false positive result may be avoided, for example, a false positive result in an assay for potassium levels in a blood sample.

[0007] In one aspect, a device is provided to which a sample may be added and prepared for hemolysis analysis. In an embodiment, the device is removably insertable into a detection system such as a spectrometer to determine a degree of hemolysis. If a degree of hemolysis in the sample is above a predetermined threshold value, an indication of the same may be provided and proper action may be taken in response to an analytical test with the same sample or a second (other) sample from the same sample source. If the sample indicates that no hemolysis exists above a predetermined threshold level, further testing of the sample may be performed with greater confidence in the results, or the results of previously run diagnostic tests may be interpreted with greater confidence.

[0008] Now referring to FIG. 1, there is shown an exemplary device 10 for hemolysis detection in a sample introduced into the device 10. In the embodiment shown, the device 10 comprises a body 12 having an upper portion 14 and a lower portion 16. The body 12 defines an opening 18 therein to allow for introduction of a sample into the device 10. The sample may be any sample suspected of having an unacceptable amount of hemolysis therein.

[0009] In the embodiment shown, the opening 18 is disposed in the upper portion 14 of the device 10, but it is understood the present invention is not so limited. Further, in the embodiment shown, a plasma separation element 20 is disposed within or carried by the body 12 of the device 10. The plasma separation element 20 is structured to isolate plasma and components from hemolysis (broken cell fragment, hemoglobin, etc.) from whole cells in a blood sample. A membrane 22 is disposed adjacent the plasma separation element 20 for receiving a plasma sample suspected of comprising an amount of hemolysis therein from the plasma separation element 20. A slit 24

is defined in the body, such as in the lower portion 16, for defining a pathway for energy to be applied to the membrane 22 from an energy source 28 as will be discussed below in order to detect an amount of hemolysis in a sample.

[0010] The body 12 of the device 10 may be formed from any suitable liquid impermeable material that is also inert to at least hemoglobin. For example, without limitation, the body 12 may be formed from a material comprising polystyrene, polyethylene, polycarbonate, polypropylene, fluoropolymer, polyester, glass, metals, ceramics, suitable composite materials, and combinations thereof as would be appreciated by those skilled in art. As noted above, one or more openings 18 may be defined in the device for introduction of a sample to the device 10. The location, number, and size (e.g., width and depth) of the one or more openings 18 may be optimized for the desired application of the device 10.

[0011] The sample for introduction into the device 10 may be one that potentially has undergone an unacceptable amount of hemolysis therein. For example, the sample may be one which could potentially create a false positive result in an assay for potassium levels by providing potassium levels which are significantly larger than the associated subject's actual potassium levels in vivo in the absence of hemolysis. For example, potassium levels inside red blood cells may be 25 times higher than in plasma. Thus, if hemolysis occurs, the potassium value of the sample in question may be increased significantly. When a subject's potassium levels are not actually as high as indicated, a false positive result may in turn result in misdiagnosis and mistreatment of a disorder characterized by elevated potassium levels. For example, as a result of hemolysis, a subject might be misdiagnosed with having hyperkalemia or any other disorder or condition characterized by elevated potassium levels, e.g., Addison's disease or hemolytic anemia. Further, the subject may be misdiagnosed as having elevated potassium levels as a side effect of taking medications such as water pills (diuretics) or blood pressure drugs and unnecessarily instructed to cease taking such medications to the subject's detriment. In addition, a false positive result could inadvertently lead to one unnecessarily being provided with agents to remove potassium from the intestines before potassium is absorbed or other unnecessary treatments. Thus, advantageously, the device 10 may be utilized in a screening process for an unacceptable level of hemolysis prior to analysis of the sample for potassium levels or for confirming the integrity of test results already run.

[0012] In certain embodiments, the sample is a whole blood sample which includes a quantity of whole blood cells, including red blood cells, white cells, and platelets. Within the sample, the extent of hemolysis may correlate to an amount of hemoglobin therein. As used herein, it is understood that the term "hemoglobin" refers to any and all hemoglobin molecules obtained either from drawn blood or by recombinant procedures in their oxygenated, deoxygenated, dimeric, tetrameric, or various polymerized forms. Hemoglobin is commonly known as the oxygen-carrying pigment and predominant protein of red blood cells. Hemoglobin is composed of four protein chains, two alpha chains and two beta chains, each with a ring-like heme group containing an iron atom. Oxygen binds reversibly to these iron atoms. In its oxygenated state, hemoglobin may be referred to as oxyhemoglobin and is characterized by a bright red. In the reduced state, hemoglobin may be referred to as deoxyhemoglobin and is characterized by a purple-blue color.

[0013] In an embodiment, a presence of hemolysis in the sample is determined by analyzing at least for an amount of oxygenated hemoglobin in the sample. In a particular embodiment, the presence of hemolysis in a sample may be determined by a degree of discoloration of the sample or brought about by contact with the sample. As such, the more red the separated plasma sample, generally, the greater the amount of hemolysis that may have taken place.

[0014] It is appreciated that prior to analysis for an extent of hemolysis, it may be desirable to prepare the plasma sample by substantially filtering out whole blood cells from the sample, particularly in the case of a whole blood sample. It is further appreciated that this may be accomplished by a number of different methods, including but not limited to centrifugation, filtration, or the like. In an embodiment, a whole blood sample is separated to produce a plasma sample comprising hemolysed cells and the contents thereof (including hemoglobin) when hemolysis has occurred in the sample.

[0015] In an aspect of the present invention, a component for separating plasma and products of hemolysis (if present) is conveniently provided in the device 10. For example, in the embodiment shown in FIG. 1, the plasma separation element 20 is included which may isolate plasma and hemolysis products, e.g., hemoglobin, from whole blood cells in a sample such as a whole blood sample. In an embodiment, the plasma separation element 20 comprises a plasma separation membrane as is commercially available in the art. In certain embodiments, the plasma separation membrane comprises an asymmetric material, which is able to retain a plurality of whole blood cells thereon while allowing plasma and small molecules/complexes to travel therethrough. A number of different plasma separation membranes are commercially available and may be suitable for use in the device 10. For example, the plasma separation membrane may comprise an asymmetric polysulfone material as is commercially available from Pall Corporation (currently under the trademark Vivid™). Alternatively, the plasma separation element 20 may comprise any other suitable material or device that can provide a sample comprising plasma and components from hemolysis (if present) therein.

[0016] In operation, a sample 20 may be introduced onto the plasma separation element 20. After an effective amount of time, which may be two minutes or less, a

retentate may be formed on the plasma separation element 20 which comprises whole blood cells, such as red blood cells, white blood cells, and platelets, while a filtrate passes through the plasma separation element 20 and onto the membrane 22. Outside the scope of the invention, a plasma portion may be formed by centrifugation or filtration remote from the device 10 and the resulting plasma portion may be introduced directly onto the membrane 22. In this instance (not according to the invention), the device 10 need not include plasma separation element 20 and the device 10 may be further modified accordingly.

[0017] The membrane 22 may be any suitable porous or non-porous material which is inert to at least hemoglobin. For example, the membrane 22 may comprise a cellulosic material, a glass fiber material, a porous polymeric material, or combinations thereof. In one embodiment, the membrane 22 comprises a filter paper having a thickness sufficient to absorb and/or maintain a sample, such as the filtrate, thereon without adding any discoloration to the sample. For example, the membrane 22 may be any suitable commercial filter paper having sufficient degree of thickness to maintain the sample thereon such as a Whatman Grade 1: 11 μm pore size; 180 μm thickness; medium flow filter paper.

[0018] According to the invention, the body 12 of the device 10 comprises a slit 24 as referred to above. The slit 24 is defined in the lower portion 16 of the device as shown in FIG. 1. The slit 24 defines a pathway for energy to be applied to the membrane 20 for the detection of hemolysis such as by spectroscopic methods. As such, the slit 24 will have a dimension, including a length and a width, suitable for a selected detection method as would be appreciated by one skilled in the art.

[0019] Referring now to FIGS. 1 and 2, the device 10 may be a component of a system 100 also comprising a detection system 26 for producing and recording an output indicative of the absence, presence, and, in certain embodiments, an extent of hemolysis in a sample introduced into the device 10. As such, the device 10 may be in a form suitable for removable insertion into or placement within the detection system 26 for analysis of the sample therein. For example, the device 10 may be in the form of a cartridge, cassette, or the like. Further, the device 10 may be formed from relatively inexpensive materials and may be readily disposable after a single use. In certain embodiments, the device 10 may be removably inserted into a corresponding receiving space 27 defined in a body of the detection system 26.

[0020] The detection system 26 may comprise any suitable apparatus for generating a qualitative, semi-quantitative, and/or quantitative result corresponding to an amount of hemolysis in the sample on the membrane 24. Thus, a detection system 26 that merely detects whether hemolysis in a sample is above a predetermined threshold is also considered to be included within the scope of the present disclosure. In a particular embodiment, the detection system 26 comprises a spectrometer as is well-known in the art comprising an energy source, a monochromator, the device 10 (when inserted), and a detector. The spectrometer is configured for scanning at least over a suitable range or at selected wavelength(s) for the detection of hemoglobin.

[0021] The amount of hemoglobin determined in a given sample is understood to be useful as a measurement of hemolysis. Thus, a threshold value for an acceptable amount of hemolysis will have an associated hemoglobin threshold value, which is readily determinable by one skilled in the art. If a sample has a hemoglobin content over the hemoglobin threshold value, it is understood that the sample may be said to have an unacceptable amount of hemolysis therein or also exhibits an amount of hemolysis over a hemolysis threshold value.

[0022] In an embodiment, as shown in FIG. 1 and 2, the detection system 26 is configured to transmit energy from the energy source 28 to the membrane 22 through the slit 24 in the device 10 once the device 10 is inserted or otherwise properly associated with the detection system 10. Thereafter, a detector 30 is provided which is configured to receive and measure energy transmitted from the membrane 22 or energy absorbed by the membrane 22. The detector 30 may comprise a photomultiplier tube (PMT), a photodiode, or a charge coupled device (CCD) as are known in the art.

[0023] The generation of a spectrometric result on the system 26 may be carried out by known methods in the art such as those described in US Published Patent Application No. 20130084592. In any case, the generated spectrum may be representative of the extent of hemolysis in the sample or on the membrane 22. In an embodiment, the extent of hemolysis may correspond empirically with a degree of coloration of the plasma fraction on the membrane 22. In a particular embodiment, an amount of oxidized hemoglobin in the sample corresponds with a degree of red coloration in the sample. The extent of hemolysis in a sample may thus be determined qualitatively, semi-quantitatively, or quantitatively through the use of known standards and controls as would be well understood by persons skilled in the art. For example, results may be compared to values of a calibration curve created from a plurality of standard samples having predetermined concentrations as is well-known in the art. According to the invention, any results on the system 26 are compared to a predetermined threshold value to determine whether hemolysis in a subject sample is greater than an acceptable limit.

[0024] For system control and data management, the detection system 26 may comprise a computing unit 32 comprising one or more modules configured to receive data from the detector 30 and determine a degree of hemolysis from the data. The computing unit may comprise, for example, a special purpose computer comprising a microprocessor, a microcomputer, an industrial controller, a programmable logic controller, a discrete logic circuit or other suitable controlling device. In an embodiment, the computing unit 32 may further comprise

one or more input channels, a memory, and output channel(s). The memory may include a computer-readable medium or a storage device, e.g., floppy disk, a compact disc read only memory (CD-ROM), or the like. In an embodiment, the computing unit 32 may comprise computer readable instructions for performing any aspect of the methods or for controlling any aspect of the components described herein.

[0025] In an embodiment, the computing unit 32 is programmed with instructions to provide an indication when determined that a degree of hemolysis in a subject sample is greater than a predetermined threshold value for hemolysis. In a particular embodiment, the predetermined threshold value is one over which would provide a potentially misleading result in a test for an analyte such as potassium. By "misleading," it is meant that the extent of hemolysis may be sufficient to alter interpretation of the result in a subsequent test for an analyte of interest. In such cases, an amount of hemolysis over the predetermined threshold may be sufficient cause a test to inaccurately reflect an amount of an analyte in question in vivo. The indication of hemolysis over a predetermined threshold may be conveyed to the test operator of the system 100 by any suitable method, such as an audio or visual alarm, or by providing the indication on a display or in a message, locally or remotely from the detection system 26. The predetermined threshold value may be, for example, an amount sufficient to provide a misleading potassium result in a subsequent test for potassium content within the same sample or a second sample which is/was taken from the same source. In a particular embodiment, the predetermined threshold value is one indicative of at least 0.5 % hemolysis in a sample. In another embodiment, the predetermined threshold value represents at least 1.0 % hemolysis. A 1% level of hemolysis, for example, may correspond to a 0.5 mmol/L increase in a potassium reading, which may lead to misdiagnosis or mistreatment.

[0026] In certain embodiments, the detection system 26 is configured for communication with an existing instrument which will test for potassium levels in a blood sample, such as a blood gas analyzer 34 (FIG. 2). Exemplary blood gas analyzers are available from Siemens Healthcare Diagnostics, Inc. and are currently sold under the trademarks: RAPIDLab 1200, RapidLab 348EX, RAPIDPoint 500, RAPIDLab 248/348, RAPIDPoint 400/405, RAPIDChem 744/754, and RAPIDPoint 340/350 Systems. In this way, the detection system 26 can act as a highly beneficial peripheral device to blood gas analyzer.

[0027] To accomplish this, the detection system 26 and blood gas analyzer 34 may comprise suitable wired or wireless connection(s) to facilitate communication therein such as a plug in connection as shown by exemplary USB connection 36. In an embodiment, a known sample from the same source (e.g., a sample taken from the same person at or about the same time) could be added to both the blood gas analyzer 34 and the detection system 26 comprising the device 10. By utilizing the detection system 26 as described herein, the detection system 26 may provide an indication that the sample introduced to the blood gas analyzer 34 is one that would likely or would be susceptible to providing misleading or less than optimal results by having a degree of hemolysis greater a predetermined threshold value. The indication may be an audio, visual, or written indication and may be output by any suitable method to any suitable location, component, report, or display. In this way, for example, samples which could potentially provide a misleading or false positive result for elevated potassium levels may be avoided or otherwise treated with appropriate caution.

[0028] Aspects of the present invention are demonstrated by the following examples, which are not intended to be limiting in any manner.

EXAMPLES

[0029] An experiment was carried out to confirm that hemolysis significantly decreases detector output (mV) as the degree of hemolysis increases. Whole blood samples with a range of 0 to 3.1 % hemolysis were used and detection was measured at 540 nm. Tables 1 and 2 and FIG. 4, for example, shows a substantially linear decrease in detector output (mV) (measured at 540 nm) from 0 % hemolysis to 3.1% hemolysis with a substantially notable plateau in the decrease of detector output from 1-2% hemolysis.

Table 1

Run #1	
Std (% Hemolysis)	Detector Output (mV)
0	495
0.1	487
1	457
1.3	454
2	459
3.1	413

Table 2

Run #2	
Std (% Hemolysis)	Detector Output (mV)
0	496
0.1	485
1	456
1.3	454
2	455
3.1	409

Claims

1. A diagnostic system comprising:

a device (10) comprising a plasma separation membrane (20) configured to separate a plasma fraction from a first blood sample by flow of the plasma fraction through the plasma separation membrane (20), wherein the plasma fraction comprises plasma and an amount of hemoglobin upon the occurrence of hemolysis in the first sample;
a detection system (26) configured for receipt of the device (10) thereon or therein and for determining the amount of hemoglobin in the plasma fraction, and,
wherein the device (10) comprises:

a body with an upper portion (14) and a lower portion (16);
an opening (18) defined in the body for introduction of the first blood sample; the plasma separation membrane (20) positioned at the upper surface of the plasma separation device (10) so as to receive the blood sample, **characterized in that**
the diagnostic system further comprises a diagnostic instrument in communication with the detection system (26) configured for analyzing a second blood sample from the same sample source for one or more analytes; and
the device (10) further comprises:

a slit (24) in the lower portion (16) of the body that defines a pathway for energy to be applied to a second membrane (22) for the detection of hemolysis;
wherein the second membrane (22) is positioned below the plasma separation membrane (20) so as to receive the plasma fraction from the plasma separation membrane (20);
the second membrane (22) comprises a filter paper having a thickness sufficient to absorb and/or maintain a sample thereon without adding any discoloration to the sample; and
the detection system (26) comprises a detector (30) for receiving and measuring energy transmitted from the membrane (22) or energy absorbed by the membrane (22).

2. The diagnostic system of claim 1, wherein the diagnostic instrument is configured to analyze the second blood sample from the same sample source for the one or more analytes only when the amount of hemoglobin in the first sample is determined to be below a predetermined threshold value for hemolysis by the detection system (26).

3. The diagnostic system of claim 2, wherein the detection system (26) is configured for plug in communication with the diagnostic instrument.

4. The diagnostic system of claim 1-3, wherein the diagnostic instrument comprises a blood gas analyzer (34).

5. The diagnostic system of claim 1-4, wherein the device (10) is in the form of a cartridge.

6. The diagnostic system of claim 1-5, wherein the detection system (26) comprises a receiving space (27) sized for receiving the device (10) therein.

7. The diagnostic system of claim 1-6, wherein the detection system (26) comprises:

an energy source (28) configured to direct energy comprising one or more wavelengths onto the second membrane (22); and
a detector (30) configured to measure one or more transmitted and/or absorbed wavelengths from the second membrane (22), the one or more transmitted and/or absorbed wavelengths indicative of an amount of hemoglobin in the plasma fraction.

8. The diagnostic system of claim 7, wherein the detection system (26) comprises a spectrometer, and wherein the spectrometer is configured to receive a transmission spectrum from the second membrane (22) upon application of the energy to the second membrane (22) from the energy source (28), and wherein the transmission spectrum is indicative of an amount of hemoglobin in the plasma fraction.

9. The diagnostic system of claim 1-8, wherein the detection system (26) further comprises a computing unit (32) configured to receive data from the detection system (26) and determine an amount of hemoglobin from the data.

10. The diagnostic system of claim 9, wherein the computing unit (32) is further configured to provide an indication that a degree of hemolysis is greater than a predetermined threshold value.

11. A method for detecting hemolysis in a whole blood sample comprising:

contacting a first blood sample with a plasma separation membrane (20) to separate a plasma fraction from the whole blood sample, the plas-

ma fraction comprising plasma and an amount of hemoglobin therein upon hemolysis of the sample,
characterized in that the method further comprises:

contacting the plasma fraction with the second membrane (22), wherein the plasma fraction is absorbed and/or maintained on the second membrane, and wherein the second membrane (22) is positioned below the plasma separation membrane (20) so as to receive the plasma fraction from the plasma separation membrane (20), and
the second membrane (22) comprises a filter paper having a thickness sufficient to absorb and/or maintain a sample thereon without adding any discoloration to the sample;
transmitting energy from the energy source (28) to the membrane (22) through the slit (24) in the device (10), wherein the slit (24) is positioned in the lower portion (16) of the body that defines a pathway for energy to be applied to a second membrane (22) for the detection of hemolysis;
determining an amount of hemoglobin in the plasma fraction through the slit (24) with a detection system (26), wherein the determining is done by a spectroscopy; and
analyzing a second sample from the same sample source as the first blood sample for an analyte in a diagnostic instrument in communication with the detection system (26), when the amount of hemoglobin in the first sample is determined to be below a predetermined threshold value for hemolysis by the detection system (26).

12. The method of claim 11, wherein the analyte comprises potassium, and wherein the analyzing is done when the amount of hemoglobin is less than a predetermined threshold value.

13. The method of claim 12, wherein the predetermined threshold value is an amount of hemolysis sufficient to provide for an elevated level of potassium in the second sample upon analysis of the second sample for potassium on the diagnostic instrument.

14. The method of claims 12 to 13, wherein the determining comprises quantitatively determining the amount of hemoglobin in the plasma fraction.

15. The method of claims 11 to 14, wherein an amount of hemolysis corresponds to the amount of hemoglobin in the plasma fraction, and wherein the method further comprises providing an indication that the amount of hemolysis is greater than a predetermined threshold value.

16. The method of claim 15, wherein the indication comprises at least one of an audio or a visual alarm.

Patentansprüche

1. Diagnosesystem, umfassend:

eine Vorrichtung (10), umfassend eine Plasmatrennmembran (20), die zum Abtrennen einer Plasmafraktion aus einer ersten Blutprobe durch Strömung der Plasmafraktion durch die Plasmatrennmembran (20) ausgelegt ist, wobei die Plasmafraktion Plasma und eine Hämoglobinmenge bei Auftreten von Hämolyse in der ersten Probe umfasst;
ein Detektionssystem (26), das zur Aufnahme der Vorrichtung (10) darauf oder darin und zur Bestimmung der Hämoglobinmenge in der Plasmafraktion ausgelegt ist, und
wobei die Vorrichtung (10) das Folgende umfasst:

einen Körper mit einem oberen Abschnitt (14) und einem unteren Abschnitt (16);
eine Öffnung (18), die im Körper zur Einführung der ersten Blutprobe definiert ist;
wobei die Plasmatrennmembran (20) an der Oberseite der Plasmatrennvorrichtung (10) angeordnet ist, um die Blutprobe aufzunehmen, **dadurch gekennzeichnet, dass** das Diagnosesystem ferner ein mit dem Detektionssystem (26) in Verbindung stehendes Diagnoseinstrument umfasst, das zur Analyse einer zweiten Blutprobe von derselben Probenquelle auf einen oder mehrere Analyten ausgelegt ist; und
wobei die Vorrichtung (10) ferner das Folgende umfasst:

einen Schlitz (24) im unteren Abschnitt (16) des Körpers, der einen Weg für Energie definiert, die zum Nachweisen von Hämolyse auf eine zweite Membran (22) aufgebracht werden soll;
wobei die zweite Membran (22) unter der Plasmatrennmembran (20) angeordnet ist, um die Plasmafraktion von der Plasmatrennmembran (20) zu erhalten;
wobei die zweite Membran (22) ein Filterpapier mit einer Dicke umfasst, die zur Absorption und/oder zum Festhalten einer Probe darauf ausreicht, ohne der Probe eine Verfärbung zuzufügen; und

wobei das Detektionssystem (26) einen Detektor (30) zum Empfangen und Messen von Energie, die von der Membran (22) übertragen wurde, oder von Energie, die von der Membran (22) absorbiert wurde, umfasst.

2. Diagnosesystem nach Anspruch 1, wobei das Diagnoseinstrument nur dann zur Analyse der zweiten Blutprobe von derselben Probenquelle auf den einen oder die mehreren Analyten ausgelegt ist, wenn vom Detektionssystem (26) festgestellt wird, dass die Hämoglobinmenge in der ersten Probe unter einem vorgegebenen Schwellenwert für Hämolyse liegt.

3. Diagnosesystem nach Anspruch 2, wobei das Detektionssystem (26) zur Plugin-Verbindung mit dem Diagnoseinstrument ausgelegt ist.

4. Diagnosesystem nach Anspruch 1-3, wobei das Diagnoseinstrument ein Blutgasanalysegerät (34) umfasst.

5. Diagnosesystem nach Anspruch 1-4, wobei die Vorrichtung (10) in Form einer Kartusche vorliegt.

6. Diagnosesystem nach Anspruch 1-5, wobei das Detektionssystem (26) einen Aufnahmeraum (27) umfasst, der eine Größe zur Aufnahme der Vorrichtung (10) darin aufweist.

7. Diagnosesystem nach Anspruch 1-6, wobei das Detektionssystem (26) das Folgende umfasst:

eine Energiequelle (28), die dazu ausgelegt ist, Energie, die eine oder mehrere Wellenlängen umfasst, auf die zweite Membran (22) zu leiten; und
einen Detektor (30), der zur Messung eines oder mehrerer von übertragenen und/oder absorbierten Wellenlängen von der zweiten Membran (22) ausgelegt ist, wobei die eine oder die mehreren übertragenen und/oder absorbierten Wellenlängen auf eine Hämoglobinmenge in der Plasmafraktion hinweisen.

8. Diagnosesystem nach Anspruch 7, wobei das Detektionssystem (26) einen Spektrometer umfasst, und wobei der Spektrometer zum Empfangen eines Transmissionsspektrums von der zweiten Membran (22) bei Aufbringen der Energie auf die zweite Membran (22) von der Energiequelle (28) ausgelegt ist, und wobei das Transmissionsspektrum auf eine Hämoglobinmenge in der Plasmafraktion hinweist.

9. Diagnosesystem nach Anspruch 1-8, wobei das Detektionssystem (26) ferner eine Computereinheit (32) umfasst, die zum Empfangen von Daten vom Detektionssystem (26) und zum Bestimmen einer Hämoglobinmenge aus den Daten ausgelegt ist.

10. Diagnosesystem nach Anspruch 9, wobei die Computereinheit (32) ferner zur Bereitstellung eines Hinweises ausgelegt ist, dass ein Hämolysegrad größer als ein vorgegebener Schwellenwert ist.

11. Verfahren zum Nachweisen von Hämolyse in einer Vollblutprobe, umfassend:
Kontaktieren einer ersten Blutprobe mit einer Plasmatrennmembran (20) zum Abtrennen einer Plasmafraktion aus der Vollblutprobe, wobei die Plasmafraktion bei Hämolyse der Probe Plasma und eine Hämoglobinmenge darin umfasst, **dadurch gekennzeichnet, dass** das Verfahren ferner das Folgende umfasst:

Kontaktieren der Plasmafraktion mit der zweiten Membran (22), wobei die Plasmafraktion auf der zweiten Membran absorbiert und/oder festgehalten wird, und wobei die zweite Membran (22) unter der Plasmatrennmembran (20) angeordnet ist, um die Plasmafraktion von der Plasmatrennmembran (20) zu empfangen, und
wobei die zweite Membran (22) ein Filterpapier mit einer Dicke umfasst, die zur Absorption und/oder zum Festhalten einer Probe darauf ausreicht, ohne der Probe eine Verfärbung zuzufügen;
Übertragen von Energie von der Energiequelle (28) auf die Membran (22) durch den Schlitz (24) in der Vorrichtung (10), wobei der Schlitz (24) im unteren Abschnitt (16) des Körpers angeordnet ist, der einen Weg für Energie definiert, die an eine zweite Membran (22) zum Nachweisen von Hämolyse angelegt werden soll;
Bestimmen einer Hämoglobinmenge in der Plasmafraktion durch den Schlitz (24) mit einem Detektionssystem (26), wobei die Bestimmung mittels einer Spektroskopie erfolgt; und
Analysieren einer zweiten Probe von derselben Probenquelle wie die erste Blutprobe auf einen Analyten in einem mit dem Detektionssystem (26) in Verbindung stehenden Diagnoseinstrument, wenn das Detektionssystem (26) feststellt, dass die Hämoglobinmenge in der ersten Probe unter einem vorgegebenen Schwellenwert für Hämolyse liegt.

12. Verfahren nach Anspruch 11, wobei der Analyt Kalium umfasst und wobei die Analyse durchgeführt wird, wenn die Hämoglobinmenge geringer als ein vorgegebener Schwellenwert ist.

13. Verfahren nach Anspruch 12, wobei der vorgegebene Schwellenwert eine Hämolysemenge ist, die zur Bereitstellung eines erhöhten Kaliumspiegels in der

zweiten Probe bei der Analyse der zweiten Probe auf Kalium am Diagnoseinstrument ausreicht.

14. Verfahren nach den Ansprüchen 12 bis 13, wobei die Bestimmung die quantitative Bestimmung der Hämoglobinmenge in der Plasmafraktion umfasst.

15. Verfahren nach den Ansprüchen 11 bis 14, wobei eine Hämolysemenge der Hämoglobinmenge in der Plasmafraktion entspricht, und wobei das Verfahren ferner die Bereitstellung eines Hinweises umfasst, dass die Hämolysemenge größer als ein vorgegebener Schwellenwert ist.

16. Verfahren nach Anspruch 15, wobei der Hinweis mindestens einen akustischen und/oder einen visuellen Alarm umfasst.

Revendications

1. Système de diagnostic comprenant :

un dispositif (10) comprenant une membrane de séparation de plasma (20) configurée pour séparer une fraction de plasma d'un premier échantillon de sang par écoulement de la fraction de plasma à travers la membrane de séparation de plasma (20), dans lequel la fraction de plasma comprend du plasma et une quantité d'hémoglobine lors de l'occurrence d'hémolyse dans le premier échantillon ;
un système de détection (26) configuré pour recevoir le dispositif (10) sur celui-ci ou dans celui-ci et pour déterminer la quantité d'hémoglobine dans la fraction de plasma, et,
dans lequel le dispositif (10) comprend :

un corps avec une partie supérieure (14) et une partie inférieure (16) ;
une ouverture (18) définie dans le corps pour l'introduction du premier échantillon de sang ;
la membrane de séparation de plasma (20) positionnée à la surface supérieure du dispositif de séparation de plasma (10) de manière à recevoir l'échantillon de sang, **caractérisée en ce que**
le système de diagnostic comprend en outre un instrument de diagnostic en communication avec le système de détection (26) configuré pour analyser un second échantillon de sang provenant de la même source d'échantillon pour un ou plusieurs analytes ; et
le dispositif (10) comprend en outre :

une fente (24) dans la partie inférieure (16) du corps qui définit un chemin d'énergie à appliquer à une seconde membrane (22) pour la détection de l'hémolyse ;
dans lequel la seconde membrane (22) est positionnée sous la membrane de séparation de plasma (20) de manière à recevoir la fraction de plasma de la membrane de séparation de plasma (20) ;
la seconde membrane (22) comprend un papier filtre ayant une épaisseur suffisante pour absorber et/ou maintenir un échantillon sur celui-ci sans ajouter aucune décoloration à l'échantillon ; et
le système de détection (26) comprend un détecteur (30) pour recevoir et mesurer l'énergie transmise par la membrane (22) ou l'énergie absorbée par la membrane (22).

2. Système de diagnostic selon la revendication 1, dans lequel l'instrument de diagnostic est configuré pour analyser le second échantillon de sang provenant de la même source d'échantillon pour ledit un ou plusieurs analytes uniquement lorsque la quantité d'hémoglobine dans le premier échantillon est déterminée comme étant inférieure à une valeur de seuil prédéterminée pour une hémolyse par le système de détection (26).

3. Système de diagnostic selon la revendication 2, dans lequel le système de détection (26) est configuré pour une communication enfichable avec l'instrument de diagnostic.

4. Système de diagnostic selon la revendication 1 à 3, dans lequel l'instrument de diagnostic comprend un analyseur de gaz de sang (34).

5. Système de diagnostic selon la revendication 1 à 4, dans lequel le dispositif (10) se présente sous la forme d'une cartouche.

6. Système de diagnostic selon la revendication 1 à 5, dans lequel le système de détection (26) comprend un espace de réception (27) dimensionné pour recevoir le dispositif (10) dans celui-ci.

7. Système de diagnostic selon la revendication 1 à 6, dans lequel le système de détection (26) comprend :

une source d'énergie (28) configurée pour diriger de l'énergie comprenant une ou plusieurs longueurs d'onde sur la seconde membrane (22) ; et
un détecteur (30) configuré pour mesurer une ou plusieurs longueurs d'onde transmises et/ou

absorbées à partir de la seconde membrane (22), la ou les longueurs d'onde transmises et/ou absorbées indiquant une quantité d'hémoglobine dans la fraction de plasma.

8. Système de diagnostic selon la revendication 7, dans lequel le système de détection (26) comprend un spectromètre, et dans lequel le spectromètre est configuré pour recevoir un spectre de transmission de la seconde membrane (22) lors de l'application de l'énergie à la seconde membrane (22) depuis la source d'énergie (28), et dans lequel le spectre de transmission indique une quantité d'hémoglobine dans la fraction de plasma.

9. Système de diagnostic selon la revendication 1 à 8, dans lequel le système de détection (26) comprend en outre une unité de calcul (32) configurée pour recevoir des données à partir du système de détection (26) et déterminer une quantité d'hémoglobine à partir des données.

10. Système de diagnostic selon la revendication 9, dans lequel l'unité de calcul (32) est en outre configurée pour fournir une indication qu'un degré d'hémolyse est supérieur à une valeur de seuil prédéterminée.

11. Procédé de détection d'hémolyse dans un échantillon de sang total comprenant les étapes consistant à :

mettre en contact un premier échantillon de sang avec une membrane de séparation de plasma (20) pour séparer une fraction de plasma de l'échantillon de sang total, la fraction de plasma comprenant du plasma et une quantité d'hémoglobine dans celui-ci lors de l'hémolyse dans l'échantillon,
caractérisé en ce que le procédé comprend en outre les étapes consistant à :

mettre en contact la fraction de plasma avec la seconde membrane (22), dans lequel la fraction de plasma est absorbée et/ou maintenue sur la seconde membrane, et dans lequel la seconde membrane (22) est positionnée sous la membrane de séparation de plasma (20) de manière à recevoir la fraction de plasma de la membrane de séparation de plasma (20), et
la seconde membrane (22) comprend un papier filtre ayant une épaisseur suffisante pour absorber et/ou maintenir un échantillon sur celui-ci sans ajouter aucune décoloration à l'échantillon ;
transmettre l'énergie de la source d'énergie (28) à la membrane (22) à travers la fente (24) dans le dispositif (10), dans lequel la fente (24) est positionnée dans la partie inférieure (16) du corps qui définit un chemin d'énergie à appliquer à une seconde membrane (22) pour la détection de l'hémolyse ;
déterminer une quantité d'hémoglobine dans la fraction de plasma à travers la fente (24) avec un système de détection (26), dans lequel la détermination est effectuée par une spectroscopie ; et
analyser un second échantillon provenant de la même source d'échantillon que le premier échantillon de sang pour un analyte dans un instrument de diagnostic en communication avec le système de détection (26), lorsque la quantité d'hémoglobine dans le premier échantillon est déterminée par le système de détection (26) comme étant inférieure à une valeur de seuil prédéterminée pour hémolyse.

12. Procédé selon la revendication 11, dans lequel l'analyte comprend du potassium, et dans lequel l'analyse est effectuée lorsque la quantité d'hémoglobine est inférieure à une valeur de seuil prédéterminée.

13. Procédé selon la revendication 12, dans lequel la valeur de seuil prédéterminée est une quantité d'hémolyse suffisante pour assurer un niveau élevé de potassium dans le second échantillon lors de l'analyse du second échantillon pour le potassium sur l'instrument de diagnostic.

14. Procédé selon les revendications 12 à 13, dans lequel la détermination comprend la détermination quantitative de la quantité d'hémoglobine dans la fraction de plasma.

15. Procédé selon les revendications 11 à 14, dans lequel une quantité d'hémolyse correspond à la quantité d'hémoglobine dans la fraction de plasma, et dans lequel le procédé comprend en outre l'indication que la quantité d'hémolyse est supérieure à une valeur de seuil prédéterminée.

16. Procédé selon la revendication 15, dans lequel l'indication comprend au moins une alarme sonore ou visuelle.

FIG. 1

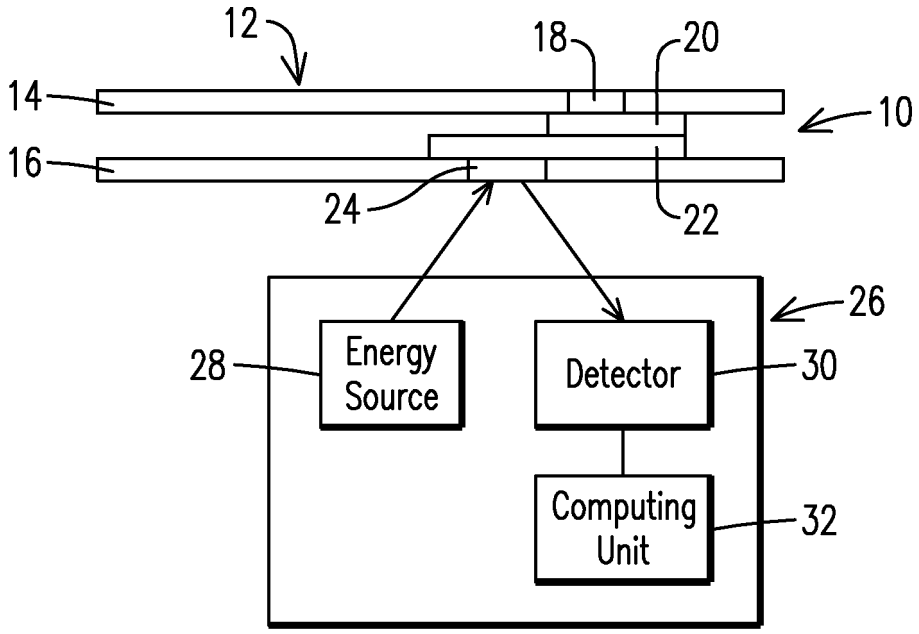
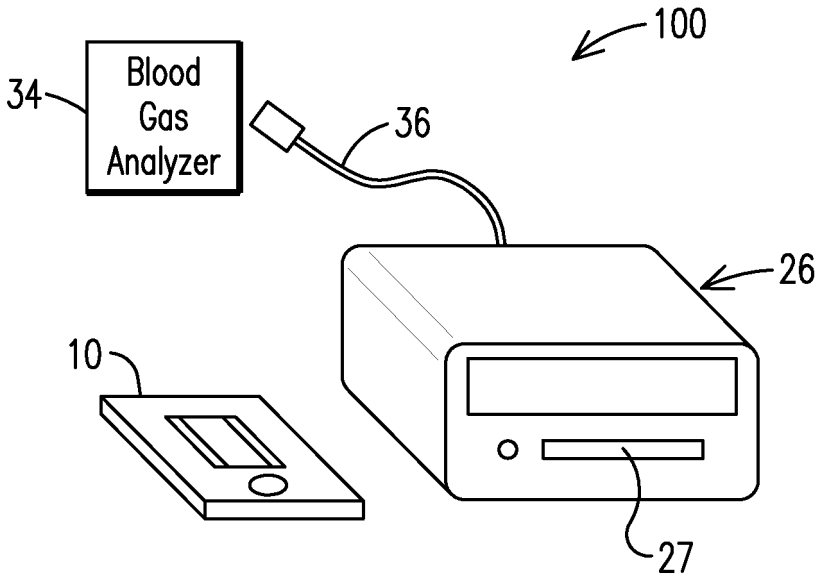

12
18
20
14
10
16
24
22
26
28
Energy Source
Detector
30
Computing Unit
32

FIG. 2


100
34
Blood Gas Analyzer
36
26
10
27

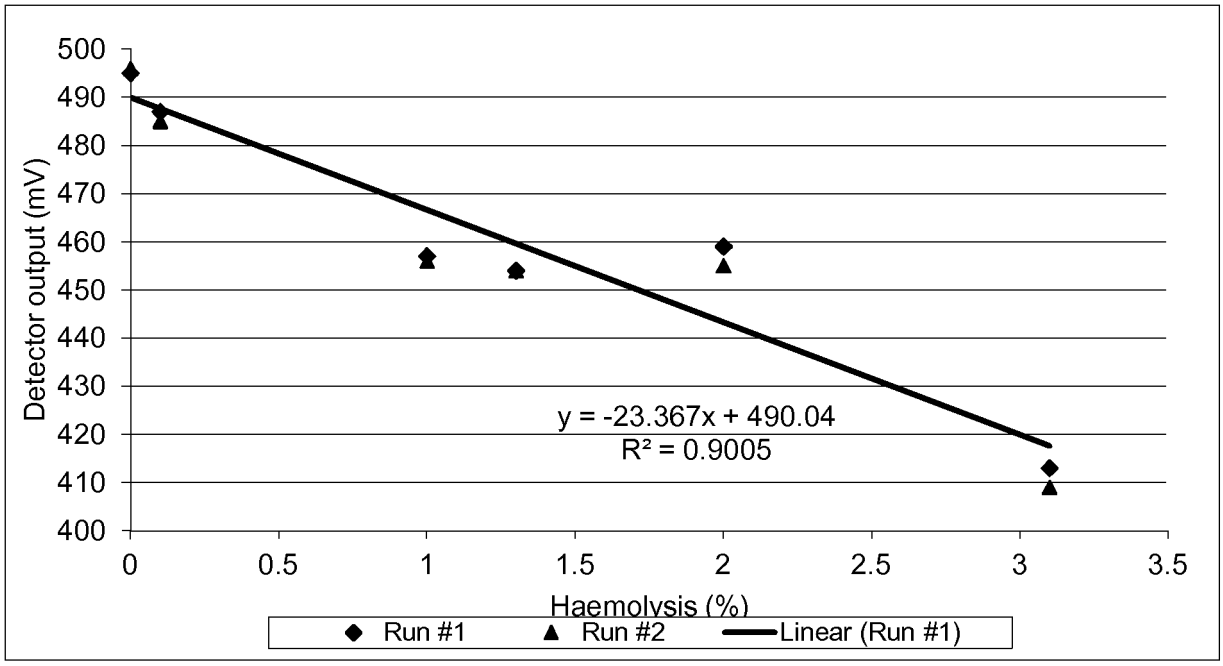

500
490
480
470
460
450
440
430
420
410
400
Detector output (mV)
0
0.5
1
1.5
2
2.5
3
3.5
Haemolysis (%)
y = -23.367x + 490.04
R² = 0.9005
Run #1
Run #2
Linear (Run #1)

FIG. 3

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 9510044 A **[0003]**
- WO 2013085462 A1 **[0003]**
- WO 20110408074 A1 **[0003]**
- WO 2012036622 A1 **[0004]**
- US 20120277697 A1 **[0004]**
- US 20130084592 A **[0023]**

Non-patent literature cited in the description

- *Clinical Chemistry,* December 2003, vol. 49 (12), 2105-2106 **[0003]**